DPC 817

Brand Name: Reverset
Drug Class: Nucleoside Reverse Transcriptase Inhibitors

Drug Description

DPC 817, also known as dexelvucitabine, is a cytidine nucleoside analogue and nucleoside reverse transcriptase inhibitor (NRTI) with specific and potent in vitro activity against HIV-1 resistant to other NRTIs. [1] [2]

HIV/AIDS-Related Uses

DPC 817 has shown specific and potent in vitro activity against HIV-1 resistant to zidovudine, lamivudine, and other NRTIs.[3] DPC 817's activity also extends to HIV resistant to both zidovudine and lamivudine, including potency against M184V and several double and triple mutations.[4]

DPC 817 was being studied in Phase IIb trials for the treatment of drug-resistant HIV infection. Development of DPC 817 has been discontinued by the licensed manufacturer, Incyte Corporation, because of increased frequency of severe hyperlipasemia in an ongoing Phase II trial. That trial, as well as enrollment for future trials, has been halted. The original manufacturer, Pharmasset, Inc., plans to analyze available data before deciding to pursue further development.[5] [6]

In the ongoing Study 203, once-daily DPC 817 doses of 100 and 200 mg were administered without concurrent cytidine analogues lamivudine or emtricitabine because monotherapy appeared to increase the efficacy of DPC 817. After 16 weeks of treatment, Grade 4 hyperlipasemia was observed in 40% of patients; 50% of patients given 200 mg doses of DPC 817 with concomitant didanosine experienced extremely elevated hyperlipasemia as well. Four cases of pancreatitis occurred in patients given 100 mg doses of DPC 817.[7] [8]

Although lower doses of DPC 817 may cause fewer adverse events, such doses have not been effective as antiretroviral therapy. Trial participants currently receiving DPC 817 should contact the trial site to discuss other available treatment options with a study investigator.[9]

Pharmacology

The investigational NRTI DPC 817 combines potency against wild-type, zidovudine-resistant, and lamivudine-resistant HIV strains with a half-life consistent with once-daily or twice-daily dosing. Like other NRTIs, DPC 817 must be phosphorylated to the active 5'-triphosphate form, DPC 817-TP. DPC 817-TP inhibits HIV reverse transcriptase (RT) by competing with the natural substrate, dC-TP.[10] The addition of fluorine at the 5-position of the pyrimidine ring increases the overall efficiency of nucleotide incorporation during both DNA- and RNA-directed synthesis. This enhanced incorporation may explain the potency of DPC 817 against HIV-1.[11] When incorporated into HIV viral DNA, DPC 817-TP causes DNA chain termination. DPC 817 is selective for inhibition of HIV RT relative to mammalian cellular DNA polymerase beta and mitochondrial DNA polymerase gamma.[12]

Almost all in vivo pharmacokinetic data available are from primate studies; rhesus monkeys were selected because nucleoside analogues generally behave similarly in rhesus monkeys and humans.[13]

Absorption of DPC 817 was variable after oral administration to rhesus monkeys; the average oral bioavailability of DPC 817 was 41%, with almost 50% of the oral dose reaching systemic circulation. The average distribution and elimination half-lives were 0.7 hours and 3.6 hours, respectively. The maximum concentration of drug in serum (Cmax) ranged from 21.1 microM to 47.5 microM, and the time to Cmax (Tmax) ranged from 1 to 4 hours with no inverse correlation between these two parameters. The highest Cmax, 47.5 microM, corresponded to a Tmax of 3 hours, whereas the lowest Cmax, 21.1 microM, corresponded to a Tmax of 1 hour.[14]

DPC 817 is scarcely bound by plasma proteins; the free fraction in human serum is 96%.[15] Absorption rates in rhesus monkeys ranged from 0.50 to 0.86 hours (averaging 0.6 hours); mean absorption times (MATs) were between 2.7 and 3.4 hours (averaging 3.1 hours). Variations in the calculated MATs after oral administration suggest

Pharmacology (cont.)

that differences in gastric emptying times may be partially responsible for the variance in the plasma concentrations achieved in these animals after oral dosing. However, other gastrointestinal tract factors have not been ruled out.[16]

After IV administration of DPC 817 to rhesus monkeys, DPC 817 could be detected in the cerebrospinal fluid (CSF) at 0.5 hours. The DPC 817 concentration in CSF did not decline noticeably for up to 3 hours after administration. Following oral administration, 2 hours elapsed before DPC 817 was detected in CSF samples. At 3 hours after oral administration, the DPC 817 concentration in CSF reached the same level as that observed 3 hours after IV administration. The apparent Cmax in CSF at 3 hours was 1.7 and 1.4 microM after oral and IV administration, respectively.[17]

The median effective concentration (EC50) of DPC 817 against HIV-1 in acutely infected human lymphocytes is 0.07 microM. After both oral and IV administration to rhesus monkeys, DPC 817 plasma and CSF concentrations were above the EC50 for HIV-1 for a prolonged period of time. High and sustained antiviral levels were attained.[18]

After IV administration of 33.3 mg/kg DPC 817 to rhesus monkeys, 76% of the original dose of DPC 817 was recovered unchanged in the urine within 8 hours. At 8 hours post oral administration, 25% of unchanged DPC 817 was recovered in the urine. Average values for renal clearance and for total systemic clearance were 0.31 l/kg/hr and 0.43 l/kg/hr, respectively. The high fraction of drug recovered in the urine indicates that DPC 817 is eliminated mainly by renal excretion.[19]

In a single dose, double-blind, Phase I study, 30 HIV infected individuals who never took DPC 817 were enrolled in a 10-day course of DPC 817 monotherapy, receiving 50 mg, 100 mg, or 200 mg DPC 817 or placebo daily. DPC 817 was highly effective, with more than 40-fold decrease in viral load. No serious adverse events were reported; all adverse events were mild or moderate and occurred at similar incidences in the active and placebo groups. The potency against HIV-1 and the remarkable safety results observed in this study, coupled with the in vitro susceptibility of drug-resistant HIV to DPC 817, suggest further investigation of the drug is warranted in treatment-experienced individuals for longer durations.[20]

Adverse Events/Toxicity

Mitochondrial toxicity has been proposed as a mechanism to explain the relatively high degree of toxicity of NRTIs. In vitro studies of DPC 817 have shown no effect on mitochondrial function.[21]

DPC 817 dosages of 100 and 200 mg daily administered as monotherapy have caused an increased incidence in Grade 4 hyperlipasemia, a marker of pancreatic inflammation. A 2% incidence of Grade 4 hyperlipasemia was observed in early evaluations of Study 203, when DPC 817 was administered with lamivudine or emtricitabine, cytidine analogues that reduced the overall effects of DPC 817. A recent evaluation of 17 patients enrolled on Study 203 and administered 200 mg of DPC 817 as monotherapy for 16 weeks identified a 40% incidence of Grade 4 hyperlipasemia. In the same study, 200 mg doses of DPC 817 administered with concurrent didanosine to 14 patients caused a 50% incidence of Grade 4 hyperlipasemia. Four cases of pancreatitis occurred in patients given 100 mg doses of DPC 817.[22] [23]

Drug and Food Interactions

DPC 817 is stable in human whole blood when incubated at 37 C for 16 hours. However, DPC 817 is unstable in acid so should be given with an antacid agent or in a buffered solution in clinical practice. Since DPC 817 is stable in human blood, no protection from acid is necessary if the compound is administered intravenously.[24]

In vitro evidence in cell culture suggests that the antiviral effects of DPC 817 on HIV are additive and in some cases synergistic with protease inhibitors, other NRTIs, and non-nucleoside reverse transcriptase inhibitors.[25]

DPC 817

Clinical Trials

For information on clinical trials that involve DPC 817, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: DPC 817 AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[26]

An intravenous form has been investigated in monkeys.[27]

Dosage Form: Enteric-coated tablets containing DPC 817 50, 100, or 200 mg, and a buffered oral solution containing DPC 817 10, 25, or 50 mg/ml are being evaluated in human trials.[28]

Chemistry

CAS Name: Cytidine, 2',3'-didehydro-2',3'-dideoxy-5-fluoro-[29]

CAS Number: 134379-77-4[30]

Molecular formula: C9-H10-F-N3-O3[31]

Stability: DPC 817 is unstable in an acidic environment. Oral preparations must be buffered, administered with an antacid, or administered in a formulation, such as enteric-coated tablets, that protects the drug from stomach acid. The IV form is stable in human blood, so no protection from acid is necessary if DPC 817 is administered intravenously.[32]

Other Names

RVT[33]

D-D4FC[34]

DFC[35]

Dexelvucitabine[36]

Further Reading

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Further Reading (cont.)

Manufacturer Information

DPC 817
Incyte Corporation
Experimental Station
Route 141 & Henry Clay Road Building E336
Wilmington, DE 19880
(302) 498-6700

Reverset
Pharmasset, Inc.
US Research Operations
1860 Montreal Road
Tucker, GA 30084
(678) 395-0035

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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